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Authors

Paolillo, Emily W
Saloner, Rowan
Montoya, Jessica L
et al.

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Frailty in Comorbid HIV and Lifetime Methamphetamine Use Disorder: Associations with Neurocognitive and Everyday Functioning

Emily W. Paolillo, M.S.[1,2], Rowan Saloner, B.S.[1,2], Jessica L. Montoya, Ph.D.[2], Laura M. Campbell, B.S.[1,2], Elizabeth C. Pasipanodya, Ph.D.[2], Jennifer E. Iudicello, Ph.D.[2], Raeanne C. Moore, Ph.D.[2,3], Scott L. Letendre, M.D.[2], Dilip V. Jeste, M.D.[2,4], & David J. Moore, Ph.D.[2]

[1]San Diego State University/University of California San Diego Joint Doctoral Program in Clinical Psychology, San Diego, California

[2]Department of Psychiatry, University of California San Diego, San Diego, California

[3]VA San Diego Healthcare System, San Diego, California

[4]Sam and Rose Stein Institute for Research on Aging, University of California San Diego, San Diego, California

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Corresponding Author:

David J. Moore, Ph.D.

Professor of Psychiatry

University of California, San Diego, HIV Neurobehavioral Research Program

220 Dickinson St, Suite B, MC8231

San Diego, CA 92103-8231

Phone: 619-543-5093

Fax: 619-543-1235

djmoore@ucsd.edu

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ABSTRACT

HIV and methamphetamine (MA) use disorder are commonly comorbid and individually-associated with adverse health consequences, including frailty; however, less is known about the combined effects of both conditions. The current cross-sectional study examined how HIV and lifetime MA use disorder relate to frailty, and explored associations between frailty and relevant clinical outcomes (i.e., neurocognitive and everyday functioning). Participants were categorized into three groups based on HIV status and lifetime MA diagnosis: HIV+/MA+ (n=43), HIV+/MA- (n=75), and HIV-/MA- (n=92). A frailty index score (representing proportion of accumulated multisystem deficits) was calculated from 27 medical and psychiatric deficits. Multiple regression was used to examine frailty index score by HIV/MA group. Additional multiple regression models examined the interaction between frailty and HIV/MA group on cognitive and everyday functioning. Comorbid HIV+/MA+ participants had higher frailty index scores than both HIV-/MA- (b=-0.13, p<.001) and HIV+/MA- participants (b=-0.06, p=.007). Additional models linked higher frailty index score to worse global neurocognition (b=-17.6, p=.018) and greater likelihood of everyday functioning dependence (OR=1.56, p=.021). Although these relationships did not significantly differ by HIV/MA status, group-stratified analyses showed that associations of frailty with neurocognitive and everyday functioning were strongest among the HIV+/MA+ group. Multimodal public health interventions aimed at reducing frailty may help to decrease the likelihood of neurocognitive and everyday functioning problems. Current findings additionally lay groundwork for future longitudinal research examining whether frailty predicts onset of neurocognitive and functional decline in individuals with comorbid HIV and MA use disorder.

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INTRODUCTION

Methamphetamine (MA) is a highly addictive psychostimulant that can detrimentally impact neurocognition, real-world functioning, and medical outcomes[1-3]. MA misuse is particularly common among persons living with HIV (PLWH) and represents a major obstacle for public health efforts aimed at reducing the prevalence and severity of HIV[4,5]. Chronic MA misuse not only enhances risk of HIV transmission, through needle-sharing and unprotected sex[6,7], but can also exacerbate HIV disease burden by disrupting antiretroviral therapy (ART) efficacy and adherence[8]. Consequently, a myriad of clinical complications can arise from comorbid HIV disease and MA use disorders (HIV+/MA+).

It has been widely documented that MA and HIV independently inflict neuropathophysiological damage, with downstream decrements in neurocognitive and everyday functioning abilities[9-11]. Although less well studied, there is also evidence to suggest that additive neurotoxic effects of MA and HIV exist and operate via the convergence of MA- and HIV-related mechanisms of neural injury to preferentially damage frontostriatal regions[12,13]. The coupling of MA misuse with HIV is characterized by neurocognitive deficits in executive functions, learning and memory, and motor skills[14-16], which can translate to impairments in real-world daily functioning. These challenges in everyday functioning typically reflect high-stakes outcomes such as unemployment, dependence in instrumental activities of daily living (IADLs), and poor antiretroviral therapy (ART) adherence[17,18]. Recent studies highlight an additive deleterious effect on everyday functioning such that HIV+/MA+ individuals exhibit the highest rates of IADL dependence compared to singly-affected groups (i.e., HIV-/MA+ and HIV+/MA-)[19]. Given the severity of impairments associated with MA misuse, a greater understanding of mechanisms underlying MA-associated neurobehavioral dysfunction is needed.

Frailty is one mechanism that may explain the detrimental effect of HIV+/MA+ on neurobehavioral impairment and has not been previously examined in this population. The construct of frailty, which first emerged through geriatric research, is conceptualized as vulnerability to multisystem damage and is most commonly used to predict risk for adverse health outcomes[20,21]. There are several different approaches to operationalizing

frailty, including as an index representing the accumulation of multisystem health deficits (e.g., diabetes, chronic inflammation, anemia) associated with the erosion of homeostatic processes[22,23]. One gerontological model for the role of frailty in neurocognition details a complex environment in which the gradual draining of physiological reserve dynamically interacts with psychosocial and functional factors to promote neurocognitive decline[24]. Given the extensive evidence that PLWH are at risk for the acquisition of multiple comorbidities potentially reflective of an accelerated aging process[25], frailty indices have been developed for PLWH across the lifespan and are predictive of mortality independent of markers of HIV disease burden[26,27].

Although the relationship between frailty and MA misuse is poorly characterized, MA misuse is linked to widespread toxicity of multiple organ systems (e.g., cardiovascular, renal, pulmonary) and enhances risk for mortality and multimorbidity[28,29]. Furthermore, models of cellular senescence provide support that the physiological dysregulation caused by MA exposure may also reflect accelerated biological aging[30]. Indications that MA and HIV independently diminish the capacity to respond to physiological stressors, coupled with gerontological evidence linking frailty to incident neurocognitive decline[31-33], necessitates the examination of frailty in the context of neurocognitive and everyday functioning among HIV+/MA+ persons.

An understanding of the temporal trends concerning MA misuse, frailty, and neurobehavioral impairment is critical for modeling their relationship. Although younger PLWH are more likely to actively use MA than older PLWH[34,35], older PLWH are more likely to exhibit frailty due to the strong relationship between frailty and age[20,22]. Thus, we aimed to study the lasting effects of past MA use disorder on frailty among middle-aged to older PLWH. Thus, the current study examined differences in frailty across three groups: a group with comorbid HIV and lifetime MA use disorder [HIV+/MA+], an HIV+/MA- group, and an HIV-/MA- control group, and explored relationships between frailty and neurocognitive and everyday functioning among the three groups. We hypothesized that the comorbid HIV+/MA+ group would demonstrate the highest frailty compared to the other two groups. We also hypothesized that frailty would be negatively associated with

neurocognitive and everyday functioning, and that these relationships would be strongest in the comorbid HIV+/MA+ group.

MATERIALS AND METHODS

Participants

Participants consisted of 118 HIV-positive (HIV+) and 92 HIV-negative (HIV-) adults, aged 35 to 65 (M=50.8, SD=7.97), enrolled in the five-year Multi-Dimensional Successful Aging among HIV-Infected Adults study conducted at the University of California, San Diego (UCSD)[36,37]. The current study represents a secondary analysis on available MA use data; thus, participants were not specifically recruited by lifetime MA status. Baseline data were included in this analysis. Study exclusion criteria were diagnosis of a psychotic disorder, presence of a neurological condition known to impact neurocognitive functioning (e.g., stroke), and positive urine toxicology for alcohol or drugs (excluding marijuana) on the day of testing. The study protocol was approved by the UCSD Institutional Review Board. Participants provided written, informed consent.

Measures

Psychiatric Assessment

The Composite International Diagnostic Interview (CIDI, v2.1) World Health [38] was administered to assess for presence of current and lifetime (occurring >12 months ago) substance use and mood disorders (e.g., major depressive disorder, MDD) based on the Diagnostic and Statistical Manual of Mental Disorders [39]. For this analysis, participants were categorized into three groups based on HIV status and lifetime methamphetamine (MA) abuse or dependence diagnosis: HIV+/MA+ (n=43); HIV+/MA- (n=75); and HIV-/MA- (n=92). No HIV- participants met criteria for lifetime MA use disorder in our available sample; therefore, our analysis is confined to the three groups identified above. Within the HIV+/MA+ group, 37 met criteria for lifetime MA dependence and 6 met criteria for lifetime MA abuse. No individuals in this sample met criteria for a current MA use disorder.

Neuromedical Assessment

Study participants completed a standardized medical history interview, which assessed for the presence of medical comorbidities (e.g., hyperlipidemia; diabetes

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mellitus) using a combination of self-report and laboratory measurements; structured neurological and medical evaluation; and collection of blood and urine samples. All participants were screened for HIV infection using a fingerstick test (Medmira, Nova Scotia, Canada) and confirmed with an Abbott RealTime HIV-1 test (Abbott Laboratories, Illinois, USA) or by submitting specimens to a Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory (ARUP Laboratories, Utah, USA) for HIV-1 viral load quantitation. Additional HIV characterization included AIDS status, plasma viral load, CD4+ T-cell counts (nadir and current), estimated duration of HIV disease, and current antiretroviral therapy (ART) regimen.

Frailty Assessment

Based on previously established methods[26,27], the frailty index was calculated as the proportion of health deficits from a group of 27 health variables, including markers of general health and comorbidities (Table 1). Thus, frailty index scores have a possible range from 0 (no deficits) to 1 (all 27 deficits).

Each variable within the frailty index was dichotomized as “1”, when a deficit was present, and “0”, when absent, based on criteria displayed in Table 1. The 27 selected variables were chosen based on all available neuromedical and neuropsychiatric data from the parent study that were consistent with variables included in previous frailty indexes[26,27]. Additionally, following published guidelines for creating a frailty index[23], we excluded factors that: 1) had greater than 5% missing data (i.e., greater than 10 missing cases in this sample), and 2) had less than 1% of participants meeting criteria for the deficit (i.e., fewer than 2 cases in this sample). Factors not included in the index due to having greater than 5% missing data in our sample included hemoglobin A1C and fasting insulin level. Factors not included in the index due to insufficient number of participants (<1%) meeting criteria for the deficit included abnormal sodium, albumin, and phosphorous levels.

Neurocognitive Assessment

Participants completed a standardized battery of neuropsychological tests to evaluate neurocognitive functioning. The battery assesses seven neurocognitive domains

commonly affected by HIV, i.e., verbal fluency, working memory, processing speed, verbal and visual learning and delayed recall, executive functioning, and motor skills[10]. Raw test scores were converted to T-scores (*M*=50; *SD*=10) adjusted to correct for age, gender, education, and race/ethnicity[40-42]. T-scores were averaged in each domain to obtain domain T-scores, and all test T-scores were averaged to obtain a Global T-score.

Everyday Functioning Assessment

In order to determine dependence in instrumental activities of daily living (IADL), participants completed a modified version of the Lawton and Brody ADL questionnaire[43]. This self-report questionnaire queried 11 IADL domains (e.g., managing finances and managing medications) and asked participants to rate their current and highest levels of functioning. Participants were categorized as IADL dependent if they reported a decline or need for assistance in ≥2 IADL domains, regardless of whether the difficulties were attributed to cognitive or physical factors. This methodology has previously been validated in a normative sample[43], and it has been shown to be associated with objective measures of functional loss in persons with HIV and/or MA use disorders[44,45].

Statistical Analyses

To compare HIV/MA groups on demographic, clinical, and primary outcome variables, one-way analysis of variance (ANOVA) was used. To follow up on significant omnibus results, pair-wise comparisons were examined using Tukey's H.S.D. ($\alpha = 0.05$) for continuous outcomes or Bonferroni-adjustments ($\alpha = 0.05/3 = 0.0167$) for dichotomous outcomes. Next, a multiple regression model was used to examine group differences in frailty, covarying for demographic and clinical factors that differed between groups. Pearson correlations were used to explore associations between frailty index score and specific MA use disorder characteristics. Last, multiple linear and logistic regressions were used to examine the interactions between frailty and HIV/MA group on global neurocognitive T-score and IADL dependence. Due to potential lack of power to find significant interaction effects, exploratory group-stratified analyses were conducted examining the relationships of frailty index score to global neurocognitive T-score and IADL dependence within each HIV/MA group. Pearson r correlations were also used to examine

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relationships between frailty and domain-specific neurocognitive functioning within the HIV+/MA+ group.

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RESULTS

Participant Characteristics

Demographic and clinical characteristics for each HIV/MA group are presented in Table 2. The HIV+/MA- group had the fewest non-Hispanic Whites, compared to the HIV+/MA+ and HIV-/MA- groups (p<.001), and the HIV+/MA+ group had fewer years of education compared to the other two groups (p<.001). PLWH (regardless of MA status) were more likely to be unemployed than persons without HIV (p<.001). Regarding neuropsychiatric characteristics, both HIV+ groups were more likely to have current and lifetime major depressive disorder (MDD) than the HIV-/MA- group (ps<.001). The HIV+/MA+ group had the highest proportion of other (non-methamphetamine) lifetime substance use disorders (SUD) (p<.001). Regarding HIV disease severity, both HIV+ groups were comparable with fairly well-controlled HIV (ps>.05). Regarding MA use disorder characteristics in the HIV+/MA+ group, participants reported meeting criteria for an MA use disorder for the first time at 34 years of age on average (SD=10.1), and most recently met criteria for an MA use disorder at 43 years of age on average (SD=8.7).

Frailty, Neurocognition, and Everyday Functioning across HIV/MA Groups

Frailty index scores, neurocognitive impairment rates and T-scores, and IADL dependence rates for each group are displayed in Table 3. In univariable analyses, frailty index score differed between all groups such that the comorbid HIV+/MA+ group had a higher mean frailty index score than the HIV+/MA- group, and the HIV+/MA- group had a higher mean frailty index score than the control group (p<.001; Figure 1). See Supplementary Table 1 for analyses exploring the proportions of participants meeting deficit criteria for individual frailty variables across each group. Regarding neurocognition, both HIV+ groups displayed worse global and executive functioning than the HIV-/MA- group (ps<.01). Compared to HIV-/MA-, the HIV+/MA- group performed worse on tests of learning, and the HIV+/MA+ group performed worse on tests of motor skills (ps<.05). Notably, the HIV+/MA+ and HIV+/MA- groups did not differ on any domain of

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neurocognitive functioning. Last, a stair-step pattern of everyday functioning by group was observed, such that the HIV+/MA+ group displayed the highest rate of IADL dependence, followed by the HIV+/MA- group, and then the control group (p<.001).

Next, a multiple linear regression analysis was conducted to further explore the differences in frailty index score across groups, covarying for specified demographic and clinical characteristics. Covariates included age (to account for the known positive relationship between frailty and age) and any characteristic that differed between groups that were not included in the creation of the frailty index: race/ethnicity, years of education, and lifetime other (non-methamphetamine) SUD. Of note, we collapsed all non-methamphetamine SUDs into one representative variable to seek parsimony in the regression models. Results of the multiple linear regression revealed that HIV/MA group membership was significantly associated with frailty index score, such that both the HIV-/MA- (b=-0.13; p<.001) and HIV+/MA- (b=-0.06; p=.007) groups had significantly lower frailty index scores than the HIV+/MA+ group (Table 4).

We also examined relationships between frailty and MA use disorder characteristics. Frailty index score was not significantly related to age at which participants first met criteria for MA use disorder (r=.08, p=.67), age at which participants most recently met criteria for MA use disorder (r=.08, p=.67), or years since last MA use disorder (r=.20, p=.26).

Relating Frailty Index Score to Neurocognitive and Everyday Functioning by HIV/MA Group

The multiple linear regression examining the interaction between frailty and HIV/MA group on global neurocognitive T-score showed a main effect of frailty, such that higher frailty index score was associated with lower global T-score (b=-17.60; p=.02; Table 5). However, there was no main effect of HIV/MA group (ps>.05) and no interaction effect between frailty and group on global T-score (ps>.05). Exploratory follow-up analyses, however, showed that the HIV+/MA+ group had the strongest negative relationship between frailty index score and global T-score (r=-.28, p=.06), followed by HIV-/MA- (r=-.17, p=.11), then HIV+/MA- (r=-.07, p=.54). Domain specific analyses within the HIV+/MA+

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group revealed that frailty index score had the strongest negative association with executive functioning (*r*=-.34, *p*=.03) and working memory (*r*=-.33, *p*=.03), followed by processing speed (*r*=-.25, *p*=.10), learning (*r*=-.21, *p*=.18), verbal fluency (*r*=-.15, *p*=.34), delayed recall (*r*=-.02, *p*=.88), and motor skills (*r*=-.01, *p*=.94).

Last, the multiple logistic regression predicting IADL dependence showed main effects of frailty index score (*b*=0.45; *OR*=1.56 [per 0.10 unit increase]; *p*=.02) and HIV/MA group, such that HIV-/MA- controls were less likely to be IADL dependent compared to the HIV+/MA+ group (*b*=-0.84; *p*=.01); however, the HIV+/MA- group was comparable to the HIV+/MA+ group (*p*>.05; Table 5). There was also no interaction between frailty index score and HIV/MA group (*p*s>.05). Exploratory follow-up analyses showed that the HIV+/MA+ group had the strongest positive relationship between frailty index score and likelihood of IADL dependence (χ^2=5.63, *OR*=2.15 [per 0.10 unit increase in frailty index score], *p*=.03), followed by HIV+/MA- (χ^2=5.56, *OR*=1.72 [per 0.10 unit increase in frailty index score], *p*=.03), then HIV-/MA- (χ^2=0.004, *OR*=1.02 [per 0.10 unit increase in frailty index score], *p*=.95).

In an effort to ensure that certain items within our frailty index were not redundant, and that results were not driven by psychosocial variables within the frailty index (i.e., unemployment and depression), we re-ran primary analyses with different variations of the frailty index. Specifically, we examined whether the stairstep effect of frailty by HIV/MA group held, and whether frailty index score still related to global neurocognition and IADL dependence. First, to ensure that items 2-5 (lipid panel values) were not redundant with item 23 (hyperlipidemia) we created new frailty indexes removing either hyperlipidemia or all lipid panel values, and all results held. Next, to ensure that lifetime MDD was not redundant with current MDD, we created new frailty indexes removing either of these, and all results held. Finally, to ensure that psychosocial variables were not driving the relationship between HIV/MA group and frailty, we removed unemployment, current MDD, and lifetime MDD from the frailty index. Although the mean frailty index score was slightly lowered among the HIV+/MA+ group (M=0.38, SD=0.10) compared to our original 27-item frailty index, the ANOVA (*p*<0.001) and post-hoc Tukey HSD (*p*s<0.05) analyses still showed a significant stairstep effect by group.

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DISCUSSION

Understanding the biological and functional consequences of HIV and lifetime MA use disorder is essential in order to provide optimal care for persons living with these conditions comorbidly. In support of our hypothesis, we found a stairstep pattern such that persons with comorbid HIV and MA use disorder had the highest frailty index scores, followed by HIV+/MA-, then HIV-/MA-. Although we did not find worse neurocognitive outcomes among those with comorbid HIV and MA compared to those with HIV only in our adult to older adult sample, there were meaningful relationships between frailty index scores and neurocognitive and everyday functioning, particularly within the comorbid group. Given prior research showing that frailty is related to future neurocognitive and functional decline among the general population[31-33], in addition to the higher levels of frailty in the comorbid group may indicate heightened risk for future neurocognitive and everyday functioning declines as individuals age; however, longitudinal research is needed to explore this hypothesis. Overall, the current results lay the groundwork for a greater understanding of the complex relationships between HIV and lifetime MA use disorder on frailty, neurocognition, and everyday functioning.

The current study is one of the first to examine frailty in the context of comorbid HIV infection and lifetime MA use disorder diagnosis. Our findings, showing highest levels of frailty among HIV+/MA+ individuals are consistent with literature examining physiological consequences of each condition independently. Several reports have documented increased frailty among PLWH compared to their seronegative counterparts[46-48], as HIV portends a heightened risk for early acquisition of age-related conditions and physiological decrements[49]. Although the effect of MA on "frailty" per se is less studied, the consequences of MA use on multiple physiological systems, including those that are captured in our frailty index, are well documented[28,29]. Our results are also consistent with research showing greater risk for physiological damage in comorbid HIV disease and other substance use (e.g., alcohol)[50]. Importantly, the association between HIV/MA group and frailty remained significant even after covarying for other factors related to frailty (i.e., age) and factors that differed between groups. Our novel results suggest that comorbid HIV and MA relates to heightened physiological damage compared

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to those with HIV only, and that damage to these physiological systems remains detectable even when MA diagnosis is remote (i.e., more than one year prior to evaluation). Further understanding of the lasting effects of past MA misuse, with and without comorbid HIV infection, on frailty is warranted.

Notably, we found that frailty index score was not significantly related to MA use disorder characteristics (i.e., age at which participants first met criteria for MA use disorder, age at which participants most recently met criteria for MA use disorder, and years since last MA use disorder) within the HIV+/MA+ group. Although we do not have data to examine the relationship between specific MA use parameters (e.g., total lifetime grams of MA used) and frailty, our finding is consistent with prior research demonstrating that characteristics of MA use do not reliably predict neurocognitive functioning[51]. Previous work indicates that such variability in the relationship between MA use and health outcomes may be explained by moderators on this relationship, including genetic susceptibility[52].

Last, we examined relationships between frailty index score and neurocognitive and everyday functioning and explored whether these relationships differ across HIV/MA groups. Consistent with hypotheses, higher frailty index score was related to worse neurocognitive functioning and greater likelihood of IADL dependence. Notably, the interaction terms within multiple regression models were not significant, indicating that the associations of frailty to neurocognitive and everyday functioning did not significantly differ by HIV/MA group; however, our exploratory within-group analyses revealed that these relationships were strongest among participants with comorbid HIV and MA. These findings support the clinical relevance of our frailty index, particularly among HIV+/MA+ individuals, and suggest that it is comprised of components that represent physiological mechanisms underlying neurobehavioral functioning in this population. For example, the frailty index is hypothesized to capture erosion of homeostatic processes (e.g., metabolic factors, chronic inflammation) that likely result in adverse neurological outcomes (e.g., apoptosis, poor cerebral perfusion)[33]. Neurocognitive domain-specific analyses within the HIV+/MA+ group further indicate that domains of executive functioning and working

memory may be especially affected by frailty, which is consistent with domains known to be impaired among individuals who are HIV+ and/or MA users[14-16].

The current study is novel in its examination of the impact of HIV and lifetime MA on frailty; however, addressing its limitations is necessary to improve the methodology of future studies. First, there were no HIV-uninfected individuals who met criteria for a lifetime MA diagnosis in our sample, and thus, we cannot conclude whether our HIV+/MA+ group findings were simply reflective of an MA effect rather than a potential combined effect. Inclusion of a HIV-/MA+ group in future research is needed to uncover whether there may be an additive or interactive effect of HIV+/MA+ on frailty. We also did not collect data on specific MA or other substance use parameters (e.g., total grams used or total days of use) for our participants. Although MA use parameters do not reliably predict neurocognitive functioning[51], future work may benefit from exploring dose-response relationships between MA and frailty. Next, we had a relatively limited sample size for HIV+/MA+ individuals. Although this limited our power to detect statistically significant interaction effects between frailty and HIV/MA group on neurocognitive and everyday functioning, we also utilized group-stratified analyses. Additionally, our frailty index, being comprised of 27 variables, contains slightly below published recommendations to include at least 30 variables to best capture relationships between health and mortality[23]; however, less than 30 variables have been used in previous frailty indices[27].

Given the heightened risk for acquired age-related declines with the increasing lifespan of PLWH, there is a need to understand factors that contribute to frailty and risk for impaired neurocognitive and everyday functioning in order to increase healthspan. Our results demonstrate that individuals with comorbid HIV and lifetime MA use disorder have high levels of frailty. Clinically, our findings highlight the need for more comprehensive medical assessment and care in this population, even when individuals do not demonstrate impairments in neurocognitive and everyday functioning. The variables included in a frailty index are often commonly collected in primary care settings, and could be compiled to evaluate risk for neurocognitive and functional decrements. Furthermore, because research among other clinical populations (e.g., older adults at risk for Alzheimer's disease) has found that frailty is associated with subsequent onset of neurocognitive and

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functional decline[33], our current findings indicate the need for future research to examine whether frailty may be a preclinical marker of subsequent neurocognitive and everyday functioning impairment among persons living with comorbid HIV and lifetime MA use disorder.

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CONFLICT OF INTEREST

None of the authors have a conflict of interest.

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(P.I.), Cristian Achim, M.D., Ph.D.; Neurovirology Component: David M. Smith, M.D. (P.I.), Douglas Richman, M.D.; International Component: J. Allen McCutchan, M.D., (P.I.), Mariana Cherner, Ph.D.; Developmental Component: Cristian Achim, M.D., Ph.D.; (P.I.), Stuart Lipton, M.D., Ph.D.; Participant Accrual and Retention Unit: J. Hampton Atkinson, M.D. (P.I.), Jennifer Marquie-Beck, M.P.H.; Data Management and Information Systems Unit: Anthony C. Gamst, Ph.D. (P.I.), Clint Cushman; Statistics Unit: Ian Abramson, Ph.D. (P.I.), Florin Vaida, Ph.D. (Co-PI), Anya Umlauf, M.S., Bin Tang, Ph.D.

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Table 1. Variables and deficit criteria for frailty index.

	Variable	Deficit Criteria
1.	High or low body mass index (BMI)	>25 or <18kg/m^2
2.	High total cholesterol	>200 mg/dl
3.	High low-density lipoprotein (LDL) cholesterol	>100 mg/dl
4.	Low high-density lipoprotein (HDL) cholesterol	<40 mg/dl
5.	High triglycerides	>150 mg/dl
6.	Abnormal white blood cell count	<4000 cells/µl
7.	Hemoglobin	Male: <13.5 µmol/l; Female: <12 µmol/l
8.	Elevated aspartate transaminase (AST)	>31 U/l
9.	Elevated alanine transaminase (ALT)	>31 U/l
10.	Abnormal alkaline phosphatase (ALP)	<38 or >126 U/l
11.	Low platelets	<150 billion/l
12.	Abnormal potassium	<3.5 or >5.3 mEq/l
13.	Elevated total bilirubin	>1.1 mg/dl
14.	C-reactive protein (CRP)	>0.7 mg/l
15.	Elevated interleukin-6 (IL-6)	>50th percentile of control sample[a]
16.	Elevated monocyte chemoattractant protein 1 (MCP-1)	>50th percentile of control sample[a]
17.	Elevated soluble CD14 (sCD14)	>50th percentile of control sample[a]

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18.	Elevated tumor necrosis factor alpha (TNF-a)	>50th percentile of control sample [a]
19.	Elevated d-dimer	>50th percentile of control sample [a]
20.	Hepatitis C (HCV)	Positive[b]
21.	Diabetes mellitus (DM)	Positive[b]
22.	Hypertension (HTN)	Positive[b]
23.	Hyperlipidemia	Positive[b]
24.	Smoking (ever)	Positive
25.	Unemployment	Positive
26.	Current major depressive disorder	Positive
27.	Lifetime major depressive disorder	Positive

[a]The control sample only includes the 92 participants who were HIV-uninfected without a lifetime history of methamphetamine use disorder (HIV-/MA-).

[b]Determined by one or a combination of sources, including self-report (if previously diagnosed by an outside provider), having a prescription medication for the condition, and/or in-laboratory blood test values indicative of the condition (HCV = standard clinical antibody detection; DM = elevated A1C or fasting glucose values; HTN = elevated systolic or diastolic blood pressure; Hyperlipidemia = elevated total cholesterol, LDL, or triglycerides).

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Table 2. Participant characteristics by HIV/MA groups (N=210).

	A HIV-/MA- (n=92)	**B** HIV+/MA- (n=75)	**C** HIV+/MA+ (n=43)	*p*-value	Pairwise Comparisons[a]
Demographics					
Age (years)	51.2 (7.45)	50.8 (8.95)	50.0 (7.35)	.74	
Sex (male)	64 (70%)	62 (83%)	37 (86%)	.04	
Race/Ethnicity (White)	64 (70%)	33 (44%)	32 (74%)	**<.001**	B < A,C
Education (years)	15.0 (2.32)	14.4 (2.61)	13.3 (2.01)	**<.001**	A,B < C
WRAT-Reading[b]	106.8 (13.78)	103.2 (14.06)	102.0 (12.89)	.09	
Unemployed	26 (28%)	48 (64%)	34 (79%)	**<.001**	A < B,C
Psychiatric Diagnoses					
Current MDD	0 (0%)	5 (7%)	8 (20%)	**<.001**	A < B,C
LT MDD	19 (21%)	34 (46%)	28 (67%)	**<.001**	A < B,C
LT other SUD[c]	33 (36%)	39 (52%)	36 (84%)	**<.001**	A < B < C
HIV Characteristics					
History of AIDS	--	46 (61%)	26 (60%)	.93	
Detectable viral load[d]	--	6 (8%)	3 (7%)	.86	
Current CD4 count[e]	--	638 [417, 901]	633 [445, 779]	.72	
Nadir CD4 count[e]	--	189 [59, 353]	150 [19, 332]	.29	
Estimated duration of infection (years)	--	17.4 (9.09)	16.6 (8.31)	.65	
On antiretroviral therapy	--	68 (93%)	43 (100%)	.08	
MA Characteristics					
Age of first MA dx	--	--	34.2 (10.05)		

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Age of most recent MA dx	--	--	42.7 (8.69)
Years since most recent MA dx	--	--	4 [2, 11]

Note. Values are presented as mean (SD), median [IQR], or N (%); WRAT-Reading = Wide Range Achievement Test, Reading subtest; LT = lifetime; MDD = major depressive disorder; SUD = substance use disorder; dx = diagnosis

[a]Pair-wise comparisons were examined using Tukey's H.S.D. ($\alpha = 0.05$) for continuous outcomes or Bonferroni-adjustments ($\alpha = 0.05/3 = 0.0167$) for dichotomous outcomes

[b]Used as an indicator of education quality

[c]Other SUDs include alcohol, cannabis, cocaine, hallucinogens, opioids, PCP, and sedatives.

[d]Plasma; Defined as >50 copies/mL

[e]Values were compared by Wilcoxon Test because of skewed distributions

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Table 3. Frailty, cognition, and everyday functioning by HIV/MA groups (N=210).

	A HIV-/MA- (n=92)	**B** HIV+/MA- (n=75)	**C** HIV+/MA+ (n=43)	*p*-value	Pairwise Comparisons[a]
Frailty					
Frailty Index Score	0.23 (0.10)	0.33 (0.12)	0.39 (0.10)	**<.001**	A < B < C
Cognition					
GDS-impaired	24 (26%)	31 (41%)	19 (44%)	.05	
Global T-score	50.1 (6.01)	47.0 (7.33)	46.8 (6.54)	**.003**	A > B,C
Verbal Fluency T-score	50.5 (6.63)	48.6 (9.27)	49.7 (6.64)	.29	
Executive Functioning T-score	52.8 (9.49)	47.7 (8.95)	47.4 (11.00)	**<.001**	A > B,C
Processing Speed T-score	52.1 (8.5)	49.0 (8.53)	48.7 (8.75)	.03	
Learning T-score	44.9 (9.22)	40.5 (9.81)	41.0 (7.79)	**.005**	A > B
Delayed Recall T-score	44.2 (9.34)	41.4 (9.97)	40.8 (8.38)	.07	
Working Memory T-score	49.4 (10.36)	48.3 (9.18)	47.5 (9.40)	.56	
Motor Skills T-score	53.5 (10.64)	50.3 (10.73)	48.4 (10.58)	**.02**	A > C
Everyday Functioning					
IADL Dependent	8 (9%)	20 (27%)	19 (44%)	**<.001**	A < B < C

Note. Values are presented as mean (SD) or N (%); GDS = global deficit score; IADL = independent activities of daily living

[a]Pair-wise comparisons were examined using Tukey's H.S.D. (α = 0.05) for continuous outcomes or Bonferroni-adjustments (α = 0.05/3 = 0.0167) for dichotomous outcomes

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Table 4. Results of multivariable linear regression predicting frailty index score.

Predictor Variables	Estimate	95% CI	*p*-value
HIV-/MA- (vs. HIV+/MA+)	-0.13	-0.17 – -0.09	**<.001**
HIV+/MA- (vs. HIV+/MA+)	-0.06	-0.10 – -0.02	**.007**
Age (years)	0.003	0.001 – 0.005	**.005**
White (vs. non-White)	0.02	-0.01 – 0.06	.142
Education (years)	-0.008	-0.015 – -0.002	**.010**
Lifetime other SUD (yes vs. no)[a]	0.001	-0.03 – 0.03	.996

Note. SUD = substance use disorder

[a]Other SUDs include alcohol, cannabis, cocaine, hallucinogens, opioids, PCP, and sedatives.

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Table 5. Results of multiple linear and logistic regressions examining the interaction between frailty and HIV/MA group on global neurocognition and everyday functioning.

Outcome: Global T-score			
Predictor Variables	**Estimate**	**95% CI**	***p*-value**
Frailty index score	-17.60	-33.62 – -1.58	**.018**
HIV-/MA- (vs. HIV+/MA+)	1.26	-1.75 – 4.27	.410
HIV+/MA- (vs. HIV+/MA+)	-1.14	-4.12 – 1.83	.448
Frailty index score * HIV-/MA-	7.05	-16.84 – 30.93	.561
Frailty index score * HIV+/MA-	13.25	-9.59 – 36.09	.254
Outcome: IADL dependence			
Predictor Variables	**Logit**	**95% CI**	***p*-value**
Frailty index score (per 0.10 unit change)	0.45	0.07 – 0.83	**.021**
HIV-/MA- (vs. HIV+/MA+)	-0.84	-1.58 – -0.21	**.014**
HIV+/MA- (vs. HIV+/MA+)	0.25	-0.33 – 0.83	.398
Frailty index score * HIV-/MA-	-0.42	-10.22 – 1.51	.155
Frailty index score * HIV+/MA-	0.10	-0.36 – 0.58	.680

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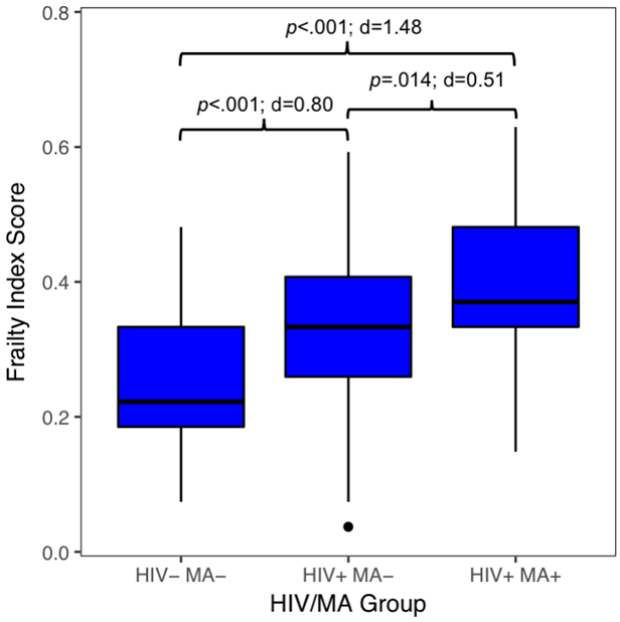

Figure 1. Frailty index score by HIV/MA group. P-values were determined using Tukey's H.S.D. for multiple comparisons.

Supplementary Table 1. Proportions of participants meeting deficit criteria for each variable comprising the frailty index across HIV/MA groups.

Frailty Index Variables	A HIV-/MA- (n=91)	B HIV+/MA- (n=72)	C HIV+/MA+ (n=43)	*p*-value	Pairwise Comparisons
BMI	65 (71%)	48 (67%)	31 (72%)	.76	
Total cholesterol	26 (29%)	18 (25%)	8 (20%)	.54	
LDL	60 (67%)	33 (46%)	20 (53%)	**.02**	A > B
HDL	16 (18%)	21 (29%)	16 (40%)	**.02**	A < C
Triglycerides	17 (19%)	28 (38%)	17 (43%)	**<.01**	A < B,C
White blood cell count	11 (12%)	7 (8%)	5 (12%)	.85	
Hemoglobin	13 (15%)	16 (22%)	7 (17%)	.46	
Hepatitis C infection	0 (0%)	11 (15%)	11 (26%)	**<.01**	A < B <C
C-reactive protein	49 (55%)	41 (67%)	24 (63%)	.30	
AST	16 (18%)	21 (29%)	14 (34%)	.08	
ALT	14 (15%)	29 (40%)	20 (49%)	**<.01**	A < B,C
Alkaline phosphate	4 (4%)	5 (7%)	4 (10%)	.50	
Platelets	1 (1%)	7 (10%)	3 (7%)	**.03**	A < B,C
Potassium	1 (1%)	6 (8%)	2 (5%)	.06	
Bilirubin	3 (3%)	7 (10%)	10 (24%)	**<.01**	A,B < C
Unemployment	26 (28%)	48 (64%)	34 (79%)	**<.01**	A < B < C
Hypertension	13 (14%)	34 (45%)	18 (42%)	**<.01**	A < B,C
Diabetes	6 (7%)	10 (13%)	4 (9%)	.33	
Smoking	10 (11%)	29 (39%)	24 (56%)	**<.01**	A < B < C
Hyperlipidemia	16 (17%)	33 (44%)	16 (37%)	**<.01**	A < B,C
IL-6	46 (50%)	28 (42%)	17 (44%)	.60	
MCP-1	46 (50%)	49 (74%)	33 (85%)	**<.01**	A < B < C
sCD14	46 (50%)	36 (55%)	27 (69%)	.13	
TNF-a	46 (50%)	36 (55%)	34 (87%)	**<.01**	A,B < C
D-dimer	46 (50%)	36 (55%)	20 (51%)	.85	

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Current MDD	0 (0%)	5 (7%)	8 (19%)	**<.01**	A < B < C
Lifetime MDD	19 (21%)	34 (45%)	28 (65%)	**<.01**	A < B < C

Note. Values are presented as N (%); MDD = major depressive disorder; Groups were compared using chi-square likelihood ratio test, or Fisher's exact test when cell count was less than five; Pair-wise comparisons were examined Bonferroni-adjustments ($\alpha = 0.05/3 = 0.0167$).

Consistent with expectations, individuals in HIV+/MA+ and/or HIV+/MA- groups were more likely to meet deficit criteria for most (15 out of 27; 56%) variables compared to the control HIV-/MA- group. Significant stairstep patterns indicating additive effects of HIV and MA on likelihood of meeting deficit criteria were found for hepatitis C infection, unemployment, smoking, current major depressive disorder (MDD), lifetime MDD, and three inflammatory biomarkers: MCP-1 and TNF-a. While calculating the proportion of total deficits in a frailty index score is clinically useful for understanding total accumulated medical burden and vulnerability, a closer examination of individual components of the frailty index may lead to a greater understanding of specific pathophysiological mechanisms underlying the association between frailty and comorbid HIV and lifetime MA use disorder. Results from the current supplemental analysis support the role of a wide range mechanisms, including co-infections, metabolic factors, behavioral/psychiatric factors, and inflammation.